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Risk factors for perineal wound infection after abdominoperineal resection of advanced lower rectal cancer

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HIGHLIGHTS

- NCRT is a risk factor for perineal wound infection after APR.
- Perineal wound infection was found in 19% of the cases after APR.
- Creativity is a key for a closure of the perineal wound infection after APR.

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ABSTRACT

Purpose: Abdominoperineal resection (APR) of advanced lower rectal cancer carries a high incidence of perineal wound infection. The aim of this study was to retrospectively evaluate risk factors for perineal wound infection after APR.

Methods: The study group comprised 154 patients who underwent APR for advanced lower rectal cancer in our department from January 1990 through December 2012. The following 15 variables were studied as potential risk factors for perineal wound infection: sex, age, body-mass index, American Society of Anesthesiologists score, diabetes mellitus, preoperative albumin level, preoperative hemoglobin level, neoadjuvant chemoradiotherapy(NCRT), surgical procedure (open surgery vs. laparoscopic surgery), operation time, bleeding volume, intraoperative transfusion, tumor diameter, invasion depth, and histopathological stage.

Results: Among the 154 patients, 30 (19%) had perineal wound infection. Univariate analysis showed that a hemoglobin level of $\leq$11 g/dL ($p = 0.001$) and NCRT ($p = 0.001$) were significantly related to perineal wound infection. On multivariate analysis including the preoperative albumin level ($\leq$3.5 g/dL) in addition to the above 2 variables, neoadjuvant chemoradiotherapy (NCRT) was the only independent risk factor for perineal wound infection. Perineal wound infection developed in 31% of patients who received NCRT, as compared with 10% of patients who did not receive NCRT. The relative risk of perineal infection in the former group was 4.092 as compared with the latter group ($p = 0.0002$).

Conclusions: NCRT is a risk factor for perineal wound infection after APR in patients with advanced lower rectal cancer.

1. Introduction

Abdominoperineal resection (APR) is used to treat conditions such as lower rectal cancer and anal canal cancer. APR is associated with a high incidence of postoperative complications, such as perineal wound infection, dehiscence, and refractory fistula [1].

Abbreviations: APR, Abdominoperineal resection; NCRT, Neoadjuvant chemoradiotherapy.

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Although such complications seriously compromise patients' quality of life, few studies have assessed the status of perineal wound infection after APR in Japan.

Perineal wound infection postoperatively develops in 10%–40% of patients who undergo APR [2,3]. General risk factors for postoperative wound infection include a high body mass index (BMI) [4], poor nutritional status [5], diabetes mellitus [6], and advanced age [7]. Surgical risk factors include a prolonged operation time [8], massive bleeding [9], and intraoperative blood transfusion [10]. To prevent wound infection, the duration of antimicrobial prophylaxis, preoperative bowel preparation, drain management, and surgical wound care should be considered. The development of wound infection causes pain and discomfort to patients, prolongs the hospital stay, and substantially increases healthcare costs. Our study demonstrated that preoperative chemoradiotherapy is a risk factor for perineal wound infection after abdominoperineal resection. Therefore, the advantages and disadvantages of currently available preoperative chemoradiotherapy for advanced lower rectal cancer should be reconsidered to establish new preventive measures. To more clearly define risk factors for perineal wound infection, we retrospectively studied patients who underwent a standard procedure for APR performed by the same team of surgeons in the same hospital and received a similar level of perioperative care.

2. Methods

The study group comprised 154 patients who underwent APR for advanced lower rectal cancer in our department from January 1990 through December 2012 (Table 1). This study was conducted only in the Department of Surgery, Kitasato University. There were no exclusion criteria for hospitals. This study was approved by the ethics committee of our hospital. Patients who underwent total pelvic exenteration or sacral resection were excluded. Perineal wound infection was evaluated according to the Guideline for Prevention of Surgical Site Infection, 1999. Patients who had pyorrhea or dehiscence of the perineal wound within 30 days after surgery were considered to have perineal wound infection.

The following 15 variables were studied as potential risk factors for perineal wound infection: sex, age, BMI, American Society of Anesthesiologists (ASA) score, diabetes mellitus, preoperative albumin level, preoperative hemoglobin level, neoadjuvant chemoradiotherapy, surgical procedure (open surgery or laparoscopy), operation time, bleeding volume, intraoperative blood transfusion, tumor diameter, invasion depth, and histopathological stage. In our study, no patient had rectal perforation. Ten patients had clinical T4 disease. After surgery, 2 patients were found to have pathological T4 disease. These patients were not excluded. Neoadjuvant chemoradiotherapy for clinical stage II to IV lower rectal cancer was started in January 2004.

Table 1
Demographic characteristics of patients.

	n = 154
Sex (male: female)	102(66%): 52(34%)
Age (years)	60.8(±10.6)
ASA score[a] (1: 2:3)	60(39%):86(56%):8(5%)
Diabetes mellitus (present: absent)	18(12%):136(88%)
Body mass index (kg/m^2)	22.2(±3.2)
NCRT[b](present: absent)	71(46%):83(54%)
Smoking (present: absent)	72(47%):82(53%)
Preoperative albumin level (g/dl)	3.9(±0.5)
Preoperative hemoglobin level (g/dl)	12.6(±2.1)
Surgical technique(open surgery:laparoscopic surgery)	139(90%):15(10%)
Operation time (min)	326.7(±83.2)
Bleeding volume (ml)	1051.9(±1182.6)
Blood transfusion (present: absent)	54(35%):100(65%)
Tumor diameter (cm)	5.1(±2.6)
pT (CR:1:2:3:4)	6(4%):2(1%):18(13%):124(81%):2(1%)
pStage (CR:I:II:III:IV)	6(4%):13(8%):57(37%):65(43%):13(8%)

[a] ASA:American society of anesthesiologists.
[b] NCRT:Neoadjuvant chemoradiotherapy.

A skin incision was made about 2 cm from the anal orifice, and the extent of resection included the anal sphincter. In our study, no patient underwent extralevator APR. As for perioperative care related to perineal wound closure, mechanical bowel preparation was performed on the day before surgery to reduce intraoperative contamination of the operative field by intestinal contents, and the anal opening was closed with a double purse-string suture immediately before surgery. All patients underwent mechanical bowel preparation. Mechanical bowel preparation was performed to prevent fecal contamination in the surgical field and to make it easier to perform surgical procedures. After proctectomy, the site of the perineal wound was washed with 3 L of warm physiological saline solution. Up to December 2003, the subcutaneous tissue of the wound was closed with a single-layer of interrupted absorbable monofilament sutures, and the skin was closed with vertical mattress sutures of the same material. From 2004 onward the skin was closed with subcuticular absorbable monofilament sutures. Since August 2006, the skin was closed with subcuticular absorbable monofilament sutures after washing the perineal wound with 1 L of warm physiological saline solution under high pressure. A closed silicone drain was placed in the floor of the lesser pelvis from the right or left hypogastric region and was removed when the drainage volume had reached 50 mL/day.

As for the antibiotic regimens during and after surgery, cefmetazole sodium was given in a dose of 1 g at the start of surgery. Additional doses were then given every 3 h and for 1–2 days after surgery.

2.1. Neoadjuvant chemoradiotherapy

2.1.1. Eligibility criteria

Eligible patients had to have previously untreated advanced lower rectal cancer, a histopathologically confirmed of adenocarcinoma, and an Eastern Cooperative Oncology Group performance status of 0–2. Other eligibility criteria were based on the seventh edition of the International Union Against Cancer (UICC) TNM Classification system. Patients also had to be 20–80 years at the time of registration and to have no severe dysfunction of main organ systems (including the spinal cord, heart, lungs, liver, and kidneys).

2.1.2. Treatment regimens

Radiotherapy was administered in fractions of 1.8 Gy per day 5 days per week for 5 consecutive weeks. The total radiation dose was 45 Gy. Computed tomography was performed to determine the planned target volume (PTV). The clinical target volume (CTV) was then determined, allowing for setup errors and organ movement. The CTV included a 1-cm margin around visible lymph nodes (macroscopic tumor volume) adjacent to the main tumor, including surrounding regions of organ and tissue invasion. The PTV was treated with a 10 MV radiation beam delivered by an accelerator in the rectum, using a 4-field box technique. The CTV of the main tumor used in our study included the perirectal lymph nodes (Fig. 1). S-1 (80 mg/m^2/day) was given orally after breakfast and dinner on days 1–5, 8 to 12, 22 to 26, and 29 to 33. Irinotecan (80 mg/m^2/day) was given as a continuous intravenous infusion over the course of 90 min on days 1, 8, 22, and 29. The chemoradiotherapy regimen included a 1-week rest period to allow

recovery from fatigue [11]. The completion rate of this regimen was 94% (67/71). Treatment was postponed in 2.8% (2/71) of the patients and was discontinued in 2.4%(2/83).

2.1.3. Statistical analysis

Statistical analysis was performed with the chi-square test and the Mann-Whitney *U* test. P values of less than 0.05 were considered to indicate significant difference. All values are expressed as means. In Table 1, all values are changed to the means. All factors with p values of less than 0.25 were included in multivariate logistic regression analysis. Data were analyzed with SPSS version 8.0 J software (SPSS, Inc., Chicago, USA).

3. Results

Perineal wound infection developed after APR in 30 (19%) of the 154 patients (Table 2). The incidence of perineal wound infection was 10.6% (7/66 cases) from 1990 through 2003 and 26.1% (23/88 cases) from 2004 through 2012 and was significantly higher during the latter period ($p = 0.0276$). From 1990 through 2003, patients ($n = 66$) patients underwent surgery alone. From 2004 through 2012, patients underwent surgery after preoperatively receiving chemoradiotherapy. Univariate analysis showed that neoadjuvant chemoradiotherapy ($p = 0.001$) and a preoperative hemoglobin level of ≤11 g/dL ($p = 0.001$) were significant risk factors for perineal wound infection (Table 3). On multivariate analysis, only neoadjuvant chemoradiotherapy ($p = 0.002$; odds ratio, 4.092) was an independent risk factor (Table 4). Perineal wound infection developed in 31% (22/71) of patients who received neoadjuvant chemoradiotherapy and 9.6% (8/83) of patients who did not. There were no flare-ups of perineal wound infection or wound dehiscence after postoperative day 30. In the subgroup of 71 patients who received neoadjuvant chemoradiotherapy, the following 6 variables did not differ significantly preoperative hemoglobin level (≤11 g/dL vs. >11 g/dL), preoperative albumin level (≤3.5 g/dL vs. >3.5 g/dL), the distance from the anal verge to the tumor (≤3 cm vs. >3 cm), the time from after treatment to surgery (≤8 weeks vs. >8 weeks), histopathological types (well-differentiated or moderately differentiated adenocarcinoma vs. others), and treatment response (grade 0, 1, 2, 3).

Table 2
Postoprative complications.

	n = 65
Perineal wound infection	30
Intestinal obstruction	20
Dysuria	7
Midline wound infection	6
Pelvic abscess	1
Portal vein thrombosis	1

Pus obtained from an infected wound was cultured in 30 patients (22 who had received neoadjuvant and 8 in the non-treatment group) and was positive for 14 (64%) of 22 patients in the treatment group and 8 (100%) of 8 patients in the non-treatment group. The most common causative organism was Enterococcus faecalis in 7 patients (32%), followed by Enterococcus cloacae in 4 (18%), *Staphylococcus* aureus in 2 (9%), Bacteroides thetaiotaomicronin 2 (9%), Bacteroides fragilis in 1 (5%), Bacteroides species in 1 (5%), and others in 3(14%). Only 6 patients (20%) had organisms sensitive to cefmetazole sodium, given as antimicrobial prophylaxis.

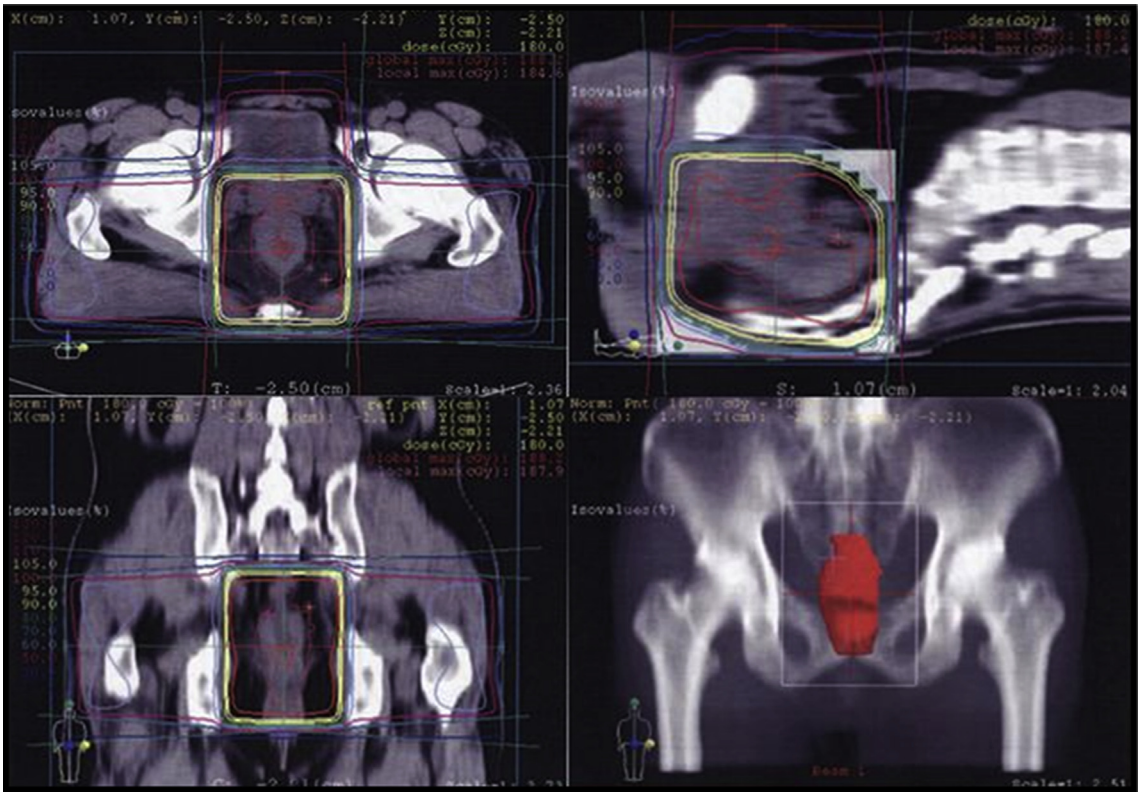

Fig. 1. The radiation fields have been described previously.

Table 3
Risk factors for perineal wound infection: univariate analysis.

	Present (n = 30)	Absent (n = 124)	p-value
Sex (male:female)	19(63%):11(37%)	83(67%):41(33%)	0.874
Age (< 65years: ≧65years)	18(60%):12(40%)	79(64%):45(36%)	0.867
ASA score(1:2,3)	14(47%):16(53%)	46(37%):78(63%)	0.449
Body mass index(kg/m^2)(< 25: ≧25)	23(77%):7(23%)	96(77%):28(23%)	0.929
Diabetes mellitus (present:absent)	5(17%):25(83%)	23(19%):101(81%)	0.809
Smoking (present:absent)	10(33%):20(67%)	56(45%):68(55%)	0.333
Preoperative albumin level (g/dl)(≦3.5:>3.5)	17(57%):13(43%)	30(24%):94(76%)	0.001
Preoperative hemoglobin level (g/dl) (≦11: > 11)	8(27%):22(73%)	15(12%):109(88%)	0.085
NCRT (present:absent)	22(73%):8(27%)	49(40%):75(60%)	0.001
Surgical technique (open surgery:laparoscopic surgery)	28(93%):2(7%)	111(90%):13(10%)	0.772
Blood transfusion(present:absent)	9(30%):21(70%)	45(36%):79(64%)	0.664
Operation times (< 300min: ≧300min)	9(30%):21(70%)	51(40%):73(60%)	0.361
Bleeding volume (ml)(< 500: ≧500)	8(27%):22(73%)	37(30%):87(70%)	0.905
Tumor diameter (< 5cm: ≧5cm)	17(57%):13(43%)	64(49%):60(51%)	0.769
pT(≦T2:T3 ≦)	5(17%):25(83%)	23(19%):101(81%)	0.809
pStage(≦II:III ≦)	17(57%):13(43%)	59(48%):65(52%)	0.490

Table 4
Maltivariate analysis.

	Odds	95%CI	p-value
NCRT(present)	4.092	1.648–10.159	0.002
Preoperative albumin level (≦3.5 g/dl)	1.883	0.619–5.724	0.265
Preoperative hemoglobin level (≦11 g/dl)	1.167	0.429–3.172	0.763

4. Discussion

Our study demonstrated that neoadjuvant chemoradiotherapy was a risk factor for perineal wound infection after APR in patients with advanced lower rectal cancer. As for the generalizability of the study, we demonstrated that preoperative chemoradiotherapy is a risk factor for perineal wound infection after abdominoperineal resection. Therefore, besides the effectiveness of currently available preoperative chemoradiotherapy for advanced lower rectal cancer, our results indicated that the advantages and disadvantages of such treatment should be reconsidered. Abdominoperineal resection is associated with a high incidence of postoperative perineal wound infection. Our study demonstrated that preoperative chemoradiotherapy is a risk factor for perineal wound infection after abdominoperineal resection. In patients with perineal wound infection, the isolated bacteria were anaerobic bacteria and gram-negative bacilli, which are enteric pathogens. In particular, the perirectal skin is highly likely to be contaminated with feces. Therefore, the skin around the anus should be carefully washed with a brush to minimize the range of fecal contamination because conventional disinfection procedures are inadequate.

Other useful countermeasures have been reported to be omentoplasty and perineal reconstruction using a pedicled myocutaneous flap. Previous studies have reported that perineal reconstruction using a pedicled myocutaneous flap may decrease the risk of perineal wound-related complications in patients who have received preoperative chemoradiotherapy. APR is postoperatively associated with a high incidence of perineal wound complications, ranging from 16% to 36% [2,3]. Resection of the rectum and anus creates a large dead space surrounded by the bone tissue at the floor of the pelvis. Exudates and blood clots are retained at this site, leading to pelvic abscess, wound infection, and fistula formation. Because tissue in the pelvis is relatively inflexible, primary closure of perineal wound creates tension, increasing the risk of wound dehiscence [1].

Bullard et al. [12] compared patients who received neoadjuvant chemoradiotherapy with those who did not and reported that the incidence of perineal wound-related complications was twofold higher in the presence of neoadjuvant chemoradiotherapy (about 47%). Other studies have likewise reported that neoadjuvant chemoradiotherapy is associated with delayed healing of the perineal wound in 47%–80% of patients [13–18]. These results suggested that radiotherapy damages not only tumors but also surrounding normal cells, causing obstructive vasculitis and delayed wound healing [19].

Chemical bowel preparation was performed since the 1970s to decrease the bacterial count in the intestine. In the 1980s, oral antimicrobial agents (kanamycin, neomycin, metronidazole, or erythromycin) were speculated to disturb the intestinal flora. Because the use of such antimicrobial agents led to an outbreak of methicillin-resistant Staphylococcus aureus (MRSA) infection, chemical bowel preparation was no longer recommended preoperatively [20]. At present, however, oral antimicrobial agents given 1 day before surgery are considered to effectively decrease the risk of surgical-site infection (SSI), without inducing resistant bacteria or microbial substitution [21–23]. Mechanical bowel preparation has been reported not to substantially alter the number of intestinal bacteria, and a multicenter randomized trial and a meta-analysis found no evidence supporting its effectiveness. Mechanical bowel preparation is therefore not recommended before elective colorectal surgery [24,25].

In the absence of antimicrobial prophylaxis, SSI develops in about 40% of patients who undergo surgery for colorectal cancer, as compared with only 11% in patients who receive appropriate antimicrobial prophylaxis [23]. Therefore, appropriate antimicrobial prophylaxis is necessary. The Guideline for Prevention of Surgical Site Infection issued by the Centers for Disease Control and Prevention recommends preoperative antimicrobial prophylaxis, supported by evidence level 1A [26]. In our series, however, only 20% of identified bacteria were sensitive to antimicrobial prophylaxis. We should therefore switch to antibacterial agents such as ampicillin sodium and sulbactam plus ampicillin sodium, which are effective against commonly isolated organisms such as enterococci and Staphylococcus aureus in the future. More than 50% of causative organisms are normal intestinal flora, and the skin around the anus can be contaminated with stools. Because conventional preoperative disinfection of the perianal skin does not eliminate all areas of contamination, the region should be washed well with a brush to minimize areas contaminated with stools [27]. The results of a meta-analysis of randomized controlled trials comparing antibacterial sutures with conventional sutures showed that the use of antibacterial sutures for wound closure decreases the risk of SSI [28,29]. Our study showed that preoperative

chemoradiotherapy is a risk factor for perineal wound infection after abdominoperineal resection. Therefore, the advantages and disadvantages of currently available regimens for preoperative chemoradiotherapy for advanced lower rectal cancer should be reconsidered, and new preventive measures are needed.

In conclusion, our results indicate that there is a high risk of perineal wound infection after APR in patients with lower rectal cancer who receive neoadjuvant chemoradiotherapy. Improved ways to prevent perineal wound infection after APR are needed.

5. Conclusion

NCRT is a risk factor for perineal wound infection after APR in patients with advanced lower rectal cancer.

Ethical approval

None required.

Sources of funding

None to declare.

Author contribution

The authors, Takatoshi Nakamura, Takeo Sato, Kazushige Hayakawa, Yoko Takayama, Masanori Naito, Takahiro Yamanashi, Atsuko Tsutsui, Hirohisa Miura, and Masahiko Watanabe, contributed to the study design, data collection, data analysis, data interpretation, and writing of the paper. Final approval of the version to be submitted was made by all the authors mentioned above.

Conflicts of interest

None to declare.

Trial registry number

None required.

Guarantor

Takatoshi Nakamura, First Author.
Masahiko Watanabe, Senior Author.

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